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Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia (Review)

McGuire W, Fowlie PW, Evans DJ

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[Intervention Review]

Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia

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ABSTRACT

Background

Studies in animal models have suggested that naloxone, a specific opiate antagonist, may improve outcomes for newborn infants with perinatal asphyxia.

Objectives

To assess the effects of naloxone versus placebo or no drug, and of single versus multiple doses of naloxone, on mortality, long term neurological problems, severity of hypoxic-ischaemic encephalopathy, and frequency of neonatal seizures in newborn infants greater than 34 weeks gestation with suspected perinatal asphyxia.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007), MEDLINE (1966 - February 2007), EMBASE (1980 - February 2007), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials comparing naloxone versus placebo, or no drug, or another dose of naloxone, in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia.

Data collection and analysis

Data was extracted using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by two authors. The pre-specified outcomes for this review were: death before hospital discharge, severe neurodevelopmental disability, severity of hypoxic-ischaemic encephalopathy, and seizures in the neonatal period.

Main results

Only one eligible randomised controlled trial was identified. This study compared the use of naloxone with placebo in newborn infants with an Apgar score of six or less at one minute after birth. There were not any data on the pre-specified outcomes for this review.

Authors' conclusions

There are insufficient data available to evaluate the safety and effectiveness of the routine use of naloxone for newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. A further randomised controlled trial is needed to determine if naloxone benefits newborn infants with suspected perinatal asphyxia. Such a trial should assess clinically important outcomes such as mortality, and adverse short and long term neurological outcomes.

PLAIN LANGUAGE SUMMARY

Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia

Newborn infants who have been deprived of oxygen before, during, or after delivery ("perinatal asphyxia") are at high risk of dying or developing brain damage. Studies in animal models suggest that over-production of the bodies' own opioids (substances similar to drugs like morphine) is detrimental. Furthermore, researchers have found that giving newborn animals with perinatal asphyxia a drug to counteract the effects of opioids (naloxone, an opioid antagonist) is beneficial. We found only one small randomised controlled trial that examined whether giving naloxone to newborn infants with suspected perinatal asphyxia improved their outcomes, but this trial did not assess the effect on death or disability. Further trials large enough to determine whether naloxone improves survival and/or reduces disability rates are therefore needed.

BACKGROUND

Perinatal asphyxia is an important cause of mortality and of acquired brain damage in newborn infants. The incidence of death or severe neurological impairment following perinatal asphyxia is about 0.5 - 1.0 per 1000 live births in resource-rich countries (Levene 1985; Thornberg 1995). In resource-poor countries, perinatal asphyxia is probably much more common and is a major cause of perinatal mortality. Data from hospital based studies in such settings suggest incidences of 5 to 50 per 1000 live births (Airede 1991; Singh 1991; Oswyn 2000). These probably represent underestimates of the true community incidence of perinatal asphyxia. Although follow up programmes are less well developed in resource-poor countries, it is likely that perinatal asphyxia produces a substantial burden of world-wide mortality and disability.

Perinatal asphyxia may occur in utero, during labour and delivery, or in the postnatal period. There are numerous causes, and the clinical manifestations vary. The International Cerebral Palsy Task Force has suggested a number of criteria to assist in the clinical diagnosis of perinatal asphyxia and to help to determine the possible underlying causes (MacLennan 1999). Of these diagnostic criteria, the two that are most relevant to the immediate clinical management in the post-natal period are:

1. Evidence of cardio-respiratory and neurological depression defined as an Apgar score less than 7 at 5 minutes. The Apgar score is most relevant for term and near term (greater than 34 weeks gestation) infants. In less mature neonates the Apgar score directly correlates with gestation and is a much less reliable indicator of perinatal asphyxia (Catlin 1986).

2. Evidence of acute hypoxic compromise with acidaemia defined as pH less than 7 or base excess greater than 12 mmol/L in umbilical arterial cord blood, or a very early neonatal blood sample. However, in many instances, and especially in resource-poor settings, an assessment of fetal or neonatal acidaemia is not available.

Signs of neonatal "hypoxic-ischaemic" encephalopathy or signs of other organ dysfunction can also be part of the case-definition of perinatal asphyxia (MacLennan 1999). However, these criteria are often not evident in the immediate post-natal period and are therefore not useful in determining the immediate post-natal management of suspected perinatal asphyxia. In fact, the aim of early intervention following suspected perinatal asphyxia is to minimise brain and other organ damage in the infant.

Brain damage associated with perinatal asphyxia occurs in two phases. Following a severe hypoxic-ischaemic event, early cell death results from primary exhaustion of the cellular energy stores. A secondary phase of programmed cell death (apoptosis) may occur several hours after the initial insult. The pathophysiology of apoptosis has been the subject of much research since there may be an opportunity to intervene following the asphyxial event to limit delayed cell death. Various pharmacological and non-pharmacological interventions that may reduce apoptosis and minimise the extent of the brain damage are the subject of other systematic reviews (Jacobs 2003; Evans 2001; Hunt 2002; Kecskes 2005).

Enhanced brain endogenous opioid release has been implicated in the pathogenesis of post-asphyxial neuronal damage. Studies in animals have suggested that endogenous opioids released following perinatal asphyxia suppress medullary inspiratory neuronal discharge and worsen the neonatal depression caused by intrauterine asphyxia (Chernick 1980). Naloxone, a specific opiate antagonist, reverses this effect (Chernick 1982). Other studies in animals have suggested that blood-brain barrier disruption is related to poor neurological outcome following perinatal asphyxia, and that naloxone prevents both the disruption and the neurological dysfunction among those survivors with intact blood-brain barriers (Ting 1994). However, naloxone has also been shown to exacerbate asphyxial brain damage in animals (Young 1984), possibly by causing inappropriate sympathomimetic surges (Padbury 1987). In a study of hypoxic newborn lambs, naloxone increased cerebral blood flow and oxygen metabolism, suggesting that endogenous opioid release protects the neonatal brain in hypoxia by diminishing the cerebral metabolic rate (Lou 1989).

The American Academy of Pediatrics (AAP) Committee on Drugs recommends that naloxone should not be used in the resuscitation of all infants who are clinically depressed at birth. The AAP advises that naloxone should be "reserved for adjunctive therapy in selected infants who have not initiated or established independent respiration following ventilation, are significantly depressed, and have a high probability of being narcotized" (AAP 1980). These recommendations refer to infants of mothers who have received opiate for analgesia up to four hours prior to delivery. The dose of naloxone recommended in 1980, 0.01 mg/kg, was later revised to 0.1 mg/kg (AAP 1990). More recently the Neonatal Resuscitation Program has further refined this advice, suggesting that naloxone should only be given to infants with 1. severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and colour, and 2. a history of maternal narcotic administration within the past four hours (NRP 2000). The effect of naloxone for narcotic exposed newborn infants is the subject of another Cochrane review (McGuire 2007). That review identified nine randomised controlled trials that compared naloxone versus placebo or no drug for newborn infants exposed to maternal narcotic analgesia prior to delivery. However, the infants recruited to those trials were not selected because of cardio-respiratory or neurological depression. In fact, infants with low Apgar scores were not eligible for inclusion in some of the trials.

Despite the above advice, there is evidence that in current neonatal practice naloxone is administered to many more newborn infants than recommended, including infants with suspected perinatal asphyxia who are not thought to have been exposed to narcotic (Herschel 2000). Given this, and the conflicting evidence from animal studies with some suggestion of adverse effects, it is important to evaluate the available data on the use of naloxone in all term and near-term newborn infants with suspected perinatal asphyxia.

OBJECTIVES

To assess the effects of naloxone versus placebo or no drug, and of single versus multiple doses of naloxone, on mortality, long term neurological problems, severity of hypoxic-ischaemic encephalopathy, and frequency of neonatal seizures in newborn infants of greater than 34 weeks gestation with suspected perinatal asphyxia.

A subgroup analysis of trials that recruited specifically infants with suspected perinatal asphyxia putatively due to narcotic exposure within four hours prior to delivery was pre-specified.

Subgroup analyses for the following dose regimens were defined prospectively:

1. Dose of naloxone less than 0.1 mg/kg body weight.
2. Dose, or cumulative dose in a multiple dose regimen, of naloxone equal to or greater than 0.1 mg/kg body weight

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials utilizing either random or quasi-random patient allocation.

Types of participants

Newborn infants of more than 34 completed weeks' gestation with suspected perinatal asphyxia, defined as clinical evidence of cardio-respiratory or neurological depression at birth as demonstrated by an Apgar score less than 7 within the first ten minutes of life, or evidence of acidaemia indicated by a pH less than 7 or base deficit greater than 12 mmol/L in umbilical arterial cord blood, or neonatal blood sample in first hour of life, or both.

Types of interventions

Trials comparing naloxone with placebo or no drug, or comparing more than one dose of naloxone, as part of the management of newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. Naloxone should have been administered within four hours of delivery.

Types of outcome measures

Primary outcomes:

1. Death prior to hospital discharge.
2. Severe neurodevelopmental disability assessed at greater than, or equal to, 12 months of age. Severe neurodevelopmental disability will be defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development: Psychomotor Developmental Index and Mental Developmental Index.

Secondary outcomes:

1. Severity of hypoxic-ischaemic encephalopathy assessed using Sarnat staging (Sarnat 1976)
2. Seizures in the neonatal period, either apparent clinically or detected by electro-encephalographic recordings

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used, including electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007), MEDLINE (1966 - February 2007), and EMBASE (1980 - February 2007). No language restriction was applied. The search strategy involved the following text words and MeSH subject headings: Asphyxia-Neonatorum/, OR asphyx*, OR enceph*, OR hypoxi*, AND Naloxone/, OR narcan, OR Narcotic antagonists/, OR narcotic, OR opiate OR opioid. The search outputs were limited with the relevant search filters for randomised controlled trials. References in previous reviews and in studies identified as potentially relevant were examined. The abstracts presented at Society for Pediatric Research and European Society for Pediatric Research, published in the journal Pediatric Research between 1984 and 2006 inclusive were handsearched. In 2002, the manufacturer of Narcan (DuPont Pharmaceuticals Company, Wilmington, Delaware 19880) was contacted to request access to data unavailable from other sources.

Data collection and analysis

1. William McGuire (WM) screened the title and abstract of all studies identified by the above search strategy. Peter Fowlie (PF) and WM screened the full text of the report of each study identified as of potential relevance. Only the studies that met all of the pre-specified inclusion criteria were included. The reviewers resolved disagreements by discussion.
2. The criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of the included trial was used. Trial quality was evaluated regarding allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. Additional information from the trial author was requested in order to clarify methodology and results.
3. A data collection form to aid extraction of relevant information and data from the included study was used. PF and WM extracted the data separately, compared data, and resolved differences by consensus.
4. The standard methods of the Cochrane Neonatal Review Group were used to analyse and synthesize the data. The treatment effects of individual trials and heterogeneity between trial results were examined using a chi-squared test for dichotomous outcomes and ANOVA for continuous outcomes. If statistical heterogeneity was detected, the possible causes were explored and sensitivity analyses were performed as appropriate. A fixed effects model for meta-analyses was used. For categorical data, effects were expressed as relative risk, risk difference, and number needed to treat, with respective 95% confidence intervals. For continuous data, the effects were expressed as weighted mean difference and 95% confidence interval.

RESULTS

Description of studies

Two studies that appeared to be relevant were identified in the first round of screening:
1. Chernick 1988 was included. The investigators undertook a blinded randomised controlled trial of naloxone versus saline placebo in newborn infants (probably term but not explicitly stated) with a one minute Apgar score of six or less. Infants whose mothers had received narcotic analgesia within four hours prior to delivery, or a general anaesthetic during delivery, were not eligible for inclusion (details in the table, Characteristics of Included Studies).The investigators obtained the informed consent of mothers pre-natally, when admitted to the labour ward, and then

recruited to the trial only those newborn infants who fulfilled the eligibility criteria. Of 193 infants with 1-minute Apgar scores of six or less, 98 received an injection of naloxone (approximately 0.4 mg/kg) and 95 received saline solution. The outcomes that were assessed in this trial were: Respiratory and heart rate up to 24 hours post intervention; time to onset of spontaneous respiration; passive and active muscle tone up to 24 hours post intervention. There are not any data available on the pre-specified outcomes for this review, either from the published report or directly from the senior investigator Professor Chernick.

2. Zhang 1996 did not fulfil all of the eligibility criteria and was excluded. The participants in the trial were infants with hypoxic ischaemic encephalopathy rather than infants with suspected perinatal asphyxia per se (details in the table, Characteristics of Excluded Studies).

The manufacturer of Narcan (DuPont Pharmaceuticals Company, Wilmington, Delaware 19880) did not have any further data.

Risk of bias in included studies

Chernick 1988 achieved good allocation concealment and blinding of intervention by assigning participants to randomly pre-numbered vials of naloxone or placebo. Follow up was complete. Only outcomes in the first 24 hours were reported. All outcomes were assessed without knowledge of whether the infant had received naloxone or saline placebo.

Effects of interventions

Chernick 1988: None of the pre-specified outcomes for this review was reported. Of the outcomes that were assessed, naloxone did not have a statistically significant effect on respiratory frequency or heart rate up to 24 hours of age. Active muscle tone of upper and lower limbs was statistically significantly increased in the naloxone group.

DISCUSSION

Only one trial that assessed the effect of naloxone for infants with suspected perinatal asphyxia was identified. This trial, published in 1988, concluded on the basis of the short term effects that naloxone "has no readily apparent benefit in the resuscitation of the asphyxiated newborn infant". Although of good methodological quality, this trial did not report on any of the pre-defined outcomes for this review. We have not found any other randomised controlled trials of this intervention. This may be because of the inherent difficulties in undertaking intervention studies in emergency situations, including the need to obtain informed consent. The included trial (Chernick 1988) addressed this specific difficulty by informing mothers of the study, and gaining their consent, when they were admitted to the labour ward. Eligible newborn infants could then receive the trial intervention without delay. The lack of other trials of this intervention may also be due to the influence of published recommendations and guidelines. For example, the American Academy of Pediatrics Committee on Drugs (AAP 1990), or the Neonatal Resuscitation Program (NRP 2000) have recommended that naloxone is only indicated for infants who have been exposed to maternal narcotic administration within four hours prior to delivery.

In addition, a randomised controlled trial of naloxone versus placebo in infants with hypoxic ischaemic encephalopathy that was undertaken in the Hebei Province People's Hospital in China in 1994 (Zhang 1996) was identified. The authors reported that the mortality rate in infants with severe hypoxic ischaemic encephalopathy was statistically significantly lower in the naloxone group than in the placebo group. However, this trial was not included because there are not any details in the published report as to whether these infants also had evidence of perinatal asphyxia as defined in the inclusion criteria for this review. The study investigators will be contacted in order to clarify this issue, and other methodological issues.

AUTHORS' CONCLUSIONS

Implications for practice

No evidence was found to support the routine use of naloxone for newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia.

Implications for research

Those who consider the evidence from animal model studies to suggest that naloxone may have a role in improving outcomes for infants with perinatal asphyxia may wish to undertake a randomised controlled trial. This trial should assess clinically important outcomes including mortality, and short and long term adverse neurological outcomes.

ACKNOWLEDGEMENTS

We thank Bolisa Zhang for translating Zhang 1996 from Chinese to English. We thank Professor Victor Chernick for clarifying some aspects of his report (Chernick 1988).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chernick 1988

Methods	Blinding of randomisation: Yes Blinding of intervention: Yes Complete follow-up: Yes Blinding of outcome measurement: Yes
Participants	Newborn infants (probably term but not explicitly stated) with one minute Apgar score 6 or less. Excluded: infants whose mothers had received narcotic analgesia within four hours of delivery, or a general anaesthetic during delivery. Teaching hospitals in Winnipeg, Canada. 1984-86.
Interventions	1. intra-muscular naloxone (0.4 mg/kg birth weight): N= 98 2. normal saline placebo : N= 95.
Outcomes	Respiratory and heart rate up to 24 hours post intervention. Time to onset of spontaneous respiration. Passive and active muscle tone up to 24 hours post intervention.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Zhang 1996	The study did not fulfil the "types of participants" eligibility criterion. Based on the translation of the original report, it seems that the population of infants studied was newborn infants with established hypoxic-ischaemic encephalopathy, rather than infants with suspected perinatal asphyxia (who are then at risk of developing hypoxic-ischaemic encephalopathy). The gestational age range of the infants in the trial is not specified.

WHAT'S NEW

Date	Event	Description
10 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2004

Date	Event	Description
20 March 2007	New search has been performed	This review updates "Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia", published in The Cochrane Library, Issue 1, 2004 (McGuire 2004). Our electronic search was updated in March 2007. No new trials were identified.
22 October 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

David Evans (DE) and William McGuire (WM) developed the protocol for this review. WM screened the title and abstract of all studies identified by the above search strategy. Peter Fowlie (PF) and WM screened the full text of the report of each study identified as of potential relevance. PF and WM extracted the data separately, compared data, and resolved differences by consensus, and with discusion with DE. DE, PF, and WM completed the final review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Ninewells Hospital and Medical School, Dundee, UK.
- Southmead Hospital, Bristol, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Asphyxia Neonatorum [*drug therapy] [mortality]; Gestational Age; Naloxone [*therapeutic use]; Narcotic Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn